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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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GRANDE BRETAGNE

PCT

File 444 · 83013
2 SEP 2004
Frank B. Dehn & Co.
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WRITTEN OPINION
(PCT Rule 66)

Date of mailing *(day/month/year)*	31.08.2004
Applicant's or agent's file reference 444.83013000	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/05659	22.12.2003	20.12.2002

International Patent Classification (IPC) or both national classification and IPC
C07H17/08, C07H17/00

Applicant
ALPHARMA APS et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☒	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 20.04.2005

DUE DATES NOTED
30/11/04

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich

Authorized Officer
Bardili, W

Formalities officer (incl. extension of time limits)

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-104 as originally filed

Claims, Numbers

1-10 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5, 10: in all respects; 8, 9: with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 8,9 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-5, 10 are so unclear that no meaningful opinion could be formed *(specify)*:

see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

see separate sheet

3. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this opinion:

☐ all parts.

☒ the parts relating to claims Nos. 6-9 .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Inventive step (IS)	Claims	6-9: no
Industrial applicability (IA)	Claims	6,7: yes

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Clarity, coverage of the search:

Claims 1-5 do not clearly define the subject-matter for which protection is sought since in the absence of any clear definition of the type of macrolide in the claims the indication *10-substituted desmethyl* has not a distinct meaning. Furthermore, the expression desmethyl does not indicate which substituents replace the methyl group. Apparently, essential information as to the structure of the claimed compounds is not present in the claim language of claims 1-5.

Claim 10 is unclear for similar reasons.

Hence, the subject-matter of claims 1-5, and 10 is not examined in respect of novelty, inventive step, and industrial applicability.

2. Medical treatment of the human body:

Claims 8 and 9 relate to medical treatment of the human body and hence to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

The application comprises four inventions:

Invention 1:
Claims 1-9 (parts): compounds as represented by formula (II), pharmaceutical compositions containing them and their use

Invention 2:
Claims 1-9 (parts): compounds as represented by formula (III), pharmaceutical compositions containing them and their use; and intermediates to prepare them according to claim 10

Invention 3:
Claims 1-9 (parts): compounds as represented by formula (IV), pharmaceutical compositions containing them and their use

Invention 4:
Claims 1-9 (parts): compounds as represented by formula (V), pharmaceutical compositions containing them and their use

(I) The application relates to a class of macrolide antibiotics which are described as *10-substituted-10-desmethyl macrolides*. The expression *10-substituted-10-desmethyl* appears to be related to a C13O lactone ring carrying further substituents (see definition at page 3 of the specification) although this is not mentioned in the claims. In the absence of any unambiguous definition of the type of macrolide in the claims the indication *10-substituted desmethyl* is given the indicated meaning.

The applicants found that in such ring systems the 10-methyl group is not necessary for the antibiotic activity and may be replaced with other substituents (see page 3). This appears to be the basic concept underlying the invention.

The international application WO-A-98 51 695 discloses macrolide antibiotics having a C13O-lactone ring which is modified at position 10, for instance by 10-ethyl (see claim 1; and table 1). Similar subject-matter is disclosed in WO-A-98 01 571, claims 1 and 29. The general concept underlying the application as indicated in the description is hence not new and cannot establish a single general inventive concept within the meaning of Rule 13.1 PCT.

(ii) The definition of the claimed compounds in claims 1-5 is incomplete since an essential part of the claimed compounds is not clearly defined by the expression "macrolide". Therefore, claim 6 comprising 4 Markush formula to define the claimed compounds is taken to examine which groups of inventions are contained in the application.

The formulae (II) to (V) do not comprise a common or special technical feature that

makes a contribution over the prior art since, as correctly expressed in the description, the substitution pattern at the ring atoms beyond C-10 in the claimed compounds is conventional and has been suggested in over 50 years (see page 2 of the description and the review article "Recent developments in 14- and 15-membered macrolides" mentioned in the search report). In particular, the 3-keto modification, the optional 6-hydroxy-substitution, the 9-keto modifications and the 11,12-ring expansion are well-known in the art (see the mentioned review article, under the appropriate heading).

Consequently four independent inventions which are not linked by a single general inventive concept are contained in the application.

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Invention 1:

WO-A-02 060 912 and in particular WO-A-98 01 571, claim 1, and WO-A-98 51 695, claim 1 and table 1, show that the 10-methyl group is not an essential requirements for C13O macrolides and in particular erythromycins of formula II to be active antibacterial agents. When wishing to provide new antibacterials a skilled person would therefore have considered replacing 10-methyl with 10-ethyl or another substituent. The claimed subject-matter is hence obvious.

Invention 2:

FR-A-2 692 579 and WO-A-98 51 695, claim 1 and table 1, show that the 10-methyl group is not an essential requirements for C13O macrolides and in particular erythromycins of formula III to be active antibacterial agents. When wishing to provide new antibacterials a skilled person would therefore have considered replacing 10-methyl with 10-ethyl or another substituent. The claimed subject-matter is hence obvious.

Invention 1 and 2:

For the assessment of the present claims 8 and 9 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.